REMARKS

Claims 1-25 are pending in the application. Claims 19 to 25 are withdrawn as being directed to non-elected subject matter. The elected claims set forth, herein, are merely to comply with the Restriction Requirement and is not to be construed as surrender of any subject matter in the instant application. Applicants hereby reserve the right to pursue the subject matter of the canceled claims in one or more divisional patent applications.

Claims 1, 3-15 have been amended to indicate that the nucleic acid is isolated to clarify the meaning of "non-naturally". Support for these amendments is found throughout the specification. Specifics are detailed below in the arguments. No new matter has been added by virtue of these amendments and entry is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112

Claims 1-18 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

Applicants respectfully traverse. However, in order to compact and expedite prosecution, Applicants have amended claims 1, 3-15. The amended claims indicate that the mitochondrial nucleic acid is recoded by substituting the mitochondrial genetic codons with the universal genetic codons. Support for this amendment is found throughout the specification. See, for example, page 22, lines 17 to 31, through to page 23, lines 1-7. Applicants teach which codons can be substituted to provide a functional ND4 mitochondrial protein, i.e. the mitochondrial nucleic acid codons. Applicants submit that one of ordinary skill in the art would not require undue experimentation to practice the instantly claimed invention based on the guidance provided in the specification. See, for example, Example 1, page 20-22, which describes the construction of recoded ND4 and methods of detection and identification of functional ND4 mitochondrial proteins. Example 2, page 22 to 26, provides the experimental data with the recoded ND4. As to the Examiner's assertions that the "nucleic acid sequences comprising a promoter with various regulatory elements that control the expression level of SEQ ID NO: 1,

and the nucleic acid sequence encoding variants of mitochondrial targeting signal will also affect the asserted biological function of the ND4 mitochondrial protein." As discussed above, Applicants describe vectors with promoters, mitochondrial targeting signals, and regulatory elements controlling the expression level of the recoded ND4 nucleic acid sequence. As such, Applicants submit that one of ordinary skill in the art would not have to perform undue experimentation to make and use the claimed invention as recited in claims 1 and 7.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claims 1-18 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants respectfully traverse. However, in order to expedite and compact prosecution claim 1 has been amended to indicate that the isolated nucleic acid comprises a nucleotide sequence encoding a functional ND4 mitochondrial protein wherein the sequence comprises at least one codon substitution of a mitochondrial codon with a non-mitochondrial codon. See, for example, page 22, lines 18-31:

> Strategy for Allotopic Expression of ND4 (Fig. 1A) - To accomplish allotopic complementation, the full-length version of nuclear-encoded ND4 was synthesized by converting the "non-standard" codons read by the mitochondrial genetic system to the universal genetic code. The nucleotide sequence of the recoded ND4 was 73% homologous to the mitochondrial version of the ND4 gene, whereas the amino acid sequences encoded by both genes were identical (Fig 1B). Therefore, the synthetic ND4 gene encodes for a "normal" ND4 protein that is identical to the ND4 protein synthesized within mitochondria. However, the recoded ND4 protein is synthesized in the cytoplasm. To direct the import of the recoded ND4 protein into the mitochondria from the cytoplasm, an MTS specifying either the N-terminal region of 1) the P1 isoform of subunit c of human ATP synthase (ATPc) containing the entire 61-amino-acid MTS plus the first 5 amino acids of the mature P1 polypeptide 24 or 2) the

aldehyde dehydrogenase (Aldh) containing the first 19 amino-acid MTS (Ni et al., J Biol Chem. 274:12685-12691, 1999) was added.

The above provides support for the claim amendment and indicates that the ND4 is recoded from the mitochondrial genetic code to the universal genetic code.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claim Rejections Under 35 U.S.C. § 102

Claims 1-3, 8-16 are rejected under 35 U.S.C. § 102(b) as being anticipated by Guy (Guy, Gene therapy for nuclear complementation of the G11778A LHON mitochondrial DNA mutation, *Neurology*, (April 24, 2001) Vol. 56, No. 8 Supplement 3, pp. A14. print. Meeting Info.: 53rd Annual Meeting of the American Academy of Neurology. Philadelphia, PA, USA. May 05-11,2001. American Academy of Neurology. CODEN: NEURAI. ISSN: 0028-3878).

Applicants respectfully traverse.

Guy neither teaches nor discloses the mutations required for a functional ND4 protein. The disclosure by Guy et al., is non-enabling and as such one of ordinary skill in the art could not construct the instant invention based on Guy et al. Furthermore, Guy et al., fails to teach an isolated nucleic acid comprising the ND4 gene. As such Guy fails to teach each and every claim limitation.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claims 1-6, and 8-18 were rejected under 35 U.S.C. § 102(a) as being anticipated by Guy et al. (Guy et al., *Ann Neuro*l 52(5): 534-42,2002, published online October 11 2002).

Applicants respectfully traverse. Guy et al., do not teach or disclose an isolated nucleic acid which encodes a functional ND4 protein. Guy *et al.* discuss a mutation, however, Guy et al., do not teach or disclose the mutations that are required as taught by Applicants. Guy et al. is a non-enabling reference for the instant invention. For example, Guy et al., refers to one mutation out of any possible number of substitutions such as those taught by Applicants. Furthermore, Applicants note that the instant application claims priority to U.S.S.N. 60/419,435 filed October 18, 2002. The cited referenced was published online, according to the Examiner, October 11, 2002. If the Examiner would prefer, Applicants can file a 37 C.F.R. § 1.131 declaration to antedate their findings and show that Applicants conceived and reduced to practice the instant invention prior to the publication date of the cited reference.

The Examiner appears to be contemplating the mechanisms of action on page 10 of the Office Action and how these would apply if "an animal model" existed is not a reason for rejection of the claims. The MPEP states in pertinent part: "Office personnel should be careful not to find evidence unpersuasive simply because no animal model for the human disease condition had been established prior to the filing of the application. See *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)."

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claims 1-2, 8, 10-12, 15-18 were rejected under 35 U.S.C. § 102(a) as being anticipated by Guy et al. (Guy et al., Gene therapy with the ND4 subunit gene recoded in the universal genetic code reverses a mitochondrial deficiency causing Leber Hereditary Optic Neuropathy (LHON), *Neurology*, (April 9, 2002) Vol. 58, No. 7 Supplement 3, pp. A508. print. Meeting Info.: 54th Annual Meeting of the American Academy of Neurology. Denver, Colorado, USA. April 13-20, 2002. CODEN: NEURAI. ISSN: 0028-3878).

Applicants respectfully traverse.

Guy *et al.*, discuss a fusion protein of ND4. The instant invention is directed to a an isolated nucleic acid comprising a nucleotide sequence encoding a functional ND4 mitochondrial protein wherein said sequence comprises at least one codon substitution of a mitochondrial codon with a nuclear codon. Guy et al., do not teach or disclose an isolated nucleic acid encoding a functional ND4 mitochondrial protein. Furthermore, Applicants can submit a declaration to show that the date of conception of the instant invention is prior to the publication date indicated in the office action.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claims 1-6, 8-18 were rejected under 35 U.S.C. §102(e) as being anticipated by Manfredi et al. (Manfredi et al., U.S. Patent Application Publication No: 2004/0072774, Publication date, April 1 5, 2004, which claims benefits of provisional application No. 60/358,935, filed on Feb. 23, 2002).

Applicants respectfully traverse.

Applicants invention is directed in part to an isolated nucleic acid comprising a nucleotide sequence encoding a functional ND4 mitochondrial protein wherein the sequence comprises at least one codon substitution of a mitochondrial codon with a nuclear codon. Applicants also teach a cell comprising the isolated nucleic acid. Manfredi discusses the introduction of a peptide into an organelle, more specifically an ATPase 6. Manfredi does not teach or disclose the instant invention. Furthermore, Manfredi does not teach or disclose each and every claim limitation of the instant invention.

In view thereof Applicants respectfully request reconsideration and withdrawal of the instant rejection.

CONCLUSION

In view of the foregoing, reconsideration and withdrawal of all rejections and allowance of the application with claims 1-18 are respectfully solicited. The amended claims set forth, herein, are merely to expedite prosecution and allowance of the application and is not to be construed as surrender of any subject matter in the instant application. If there are any remaining issues or the Examiner believes that a telephone conversation with the Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at telephone number shown below.

Although, Applicants believe that no extensions of time are required with submission of this paper, Applicants request that this submission also be considered as a petition for any further extensions of time if necessary. The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for any retroactive extensions of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to Deposit Account No. 50-0951.

Respectfully submitted,
AKERMAN SENTERFITT

Date: March 19, 2007

Nicholas A. Zachariades, Ph.D.
Reg. No. 56,712
AKERMAN SENTERFITT
P.O. Box 3188
West Palm Beach, FL 33402-3188
Tel: 561-653-5000

Docket No. 5853-324